

Specification

Antitumor Protein and Gene Encoding Same

5 BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to an antitumor protein and an nucleotide sequence encoding the same.

Background Art

10 Various studies have been conducted on antitumor substances found in edible mushrooms.

For example, polysaccharides and glycoprotein from mushrooms which have antitumor activity are disclosed in Japanese Patent Laid-open Publication Nos.61214/1977, 15 74797/1980, 293923/1986, 70362/1993 and 80699/1994, Japanese Patent Publication Nos. 47518/1986, 47519/1986 and 26172/1991. It is also reported that mushrooms are found to have antitumor activity when administered.

20 However, there has been no report on an amino acid sequence of an antitumor protein derived from Tricholoma matsutake which directly kills a tumor cell and on a gene encoding said protein.

SUMMARY OF THE INVENTION

25 The inventors now have purified an antitumor protein derived from Tricholoma matsutake and determined an amino acid sequence as well as a cDNA sequence encoding the protein. Further, the inventors have successfully purified the cDNA sequence and obtained a recombinant antitumor protein expressed in E. coli which is transformed by 30 introducing a vector comprising the cDNA sequence. The present invention is based on these findings.

Thus, an object of the present invention is to provide an antitumor protein, a fragment of said protein, a nucleotide molecule encoding said protein, a vector 35 comprising said molecule, a host cell transformed by said vector, a process for preparing said protein, and an antibody against said protein.

The protein according to the present invention comprises

(a) an amino acid sequence of SEQ ID No.1, or  
(b) a modified amino acid sequence of SEQ ID No.1 which has antitumor activity wherein one or more amino acids are added and/or inserted into the amino acid sequence of SEQ ID No.1 and/or one or more amino acids in the amino acid sequence of SEQ ID No.1 are substituted and/or deleted.

The protein according to the present invention is useful as an antitumor agent.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the structure of plasmid vector pTS18.

Figure 2 illustrates the deletion of the TTM gene. Dashed lines denote a deleted area.

#### DETAILED DESCRIPTION OF THE INVENTION

##### Protein

The protein according to the present invention comprises the amino acid sequence of SEQ ID No.1. A protein consisting of the amino acid sequence of SEQ ID No.1 has antitumor activity as described in examples.

Examples of the proteins according to the present invention include those consisting of a modified amino acid sequence of SEQ ID No.1 which has antitumor activity wherein one or more amino acids are added and/or inserted into the amino acid sequence of SEQ ID NO.1 and/or one or more amino acids in the amino acid sequence of SEQ ID NO.1 are substituted and/or deleted. The terms "addition", "insertion", "substitution" and "deletion" refer to those which do not damage the antitumor activity of the protein consisting of the amino acid sequence of SEQ ID NO.1. The numbers of modifications such as additions, insertions, substitutions and deletions may be in the range between 1 and 8.

An addition, insertion, substitution or deletion may be introduced into an amino acid sequence in accordance with, for example, Molecular Cloning (A laboratory manual),

second edition, Cold Spring Harbor Laboratory Press, Vol. 2, Chap. 15 (1989); Botstein, D. et al., Science, 229:1193 (1985); Craik, C.S., Bio. Techniques, 3:12 (1985); Itakura, K. et al., Annu. Rev. Biochem. 53:323 (1984); Shortle, D. et al., Annu. Rev. Genet. 15:265 (1981); or Smith, M. Annu. Rev. Genet. 19:423 (1985).

The wording "protein which have antitumor activity" as used herein refers to a protein which is evaluated by one skilled in the art to have antitumor activity, for example, a protein which is evaluated to have antitumor activity as tested under the conditions in Example 1 (3).

The molecular weight of the protein consisting of the amino acid sequence of SEQ ID NO.1 is about 65 kDa as measured by SDS-PAGE.

The amino acid sequence of SEQ ID NO.1 can be prepared by expression of the DNA sequence of SEQ ID NO.2 in a bacteria using a common technique. The cDNA sequence can be prepared by screening a cDNA library derived from Tricholoma matsutake using an antibody against the antitumor protein as a probe (see Example 2).

The protein according to the present invention has antitumor activity. Therefore, the protein according to the present invention may be formulated in a pharmaceutical composition which is used in the treatment of tumor such as carcinoma of uterine cervix or corpus uteri, and a variety of cancers caused by abnormal expression of antioncogene p53 or pBR (e.g., carcinoma cutaneum, lung cancer, liver cancer, kidney cancer, and breast cancer).

The pharmaceutical composition according to the present invention may be administered to a mammal including a human perorally or parenterally (e.g., intramuscularly, intravenously, subcutaneously, intrarectally, percutaneously or pernasally) in a form suitable for peroral or parenteral administration. A formulation which directly reaches a target area (e.g., a tablet which dissolves at a specific site, a liniment, or an injection) may be preferably used in the treatment of tumor.

The protein according to the present invention may be formulated in oral drugs (e.g., tablets, capsules, granules, powder, pills, grains, troches) when considering stability of the protein and the drug delivery path; injectable drugs (e.g., for intravenous or intramuscular injection); intrarectal drugs; and soluble or insoluble suppositories depending on its intended use. The pharmaceutical composition in these forms may be prepared by conventional methods with pharmaceutically acceptable vehicles such as bulking agents and fillers; adjuvants such as binding agents, wetting agents, disintegrants, surfactants, lubricants, dispersers, buffering agents, and solution adjuvant; additives such as preservatives, antiseptics, flavouring agents, soothing agents, stabilizers, colouring agents, and sweetening agents. A dose for various treatments may be determined depending on the route of administration as well as the age, sex, and condition of the patient.

#### Nucleotide Sequence

The present invention provides a nucleotide sequence encoding the protein according to the present invention. Examples of such nucleotide sequences include those comprising all or part of the DNA sequence of SEQ ID NO.2. Other examples of such nucleotide sequences include those comprising all or part of the DNA sequence in SEQ ID NO.2.

As mentioned above, the DNA sequence of SEQ ID NO.2 was obtained from a cDNA library derived from Tricholoma matsutake. This DNA sequence contains an open reading frame of the protein which starts at ATG (1-3) and ends at TAA (1699-1701).

The amino acid sequence determines a number of possible base sequences that encode the amino acid sequence in SEQ ID NO.1.

When the amino acid sequence of the protein according to the present invention is given, a nucleotide sequence encoding the amino acid sequence is easily determined, and a variety of nucleotide sequences encoding the amino acid

sequence of SEQ ID NO: 1 can be selected.

Thus, a nucleotide sequence encoding the protein according to the present invention include DNA sequences which degenerate as a result of the genetic code as to the  
5 DNA sequence of SEQ ID No.2 as well as RNA sequences corresponding to the DNA sequences.

The nucleotide sequence according to the present invention may be naturally occurred or obtained by synthesis. It may also be synthesized with a part of a  
10 sequence derived from the naturally occurring one. DNAs may typically be obtained by screening a chromosome library or a cDNA library in accordance with conventional methods in the field of genetic engineering, for example, by screening a chromosome library or a cDNA library with an appropriate  
15 DNA probe obtained based on information of the partial amino acid sequence. The nucleotide sequence according to the present invention can be prepared, for example, from Tricholoma matsutake cDNA library by using an oligonucleotide encoding a peptide selected from SEQ ID  
20 Nos.3-18 as a screening probe.

The nucleotide sequences from nature are not specifically restricted to any sources; but may be derived from Tricholoma matsutake or other sources.

#### Vectors and Transformed Cells

25 The present invention provides a vector comprising the nucleotide sequence according to the present invention in such a manner that the vector can be replicable and express the protein encoded by the nucleotide sequence in a host cell. In addition, according to the present invention, we  
30 provide a host cell transformed by the vector. There is no other restriction to the host-vector system. It may express proteins fused with other proteins. Examples of an expression system of a fusion protein include those expressing MBP (maltose binding protein), GST (glutathione-S-transferase), HA (hemagglutinin), polyhistidine, myc, and Fas.  
35

Examples of such systems expressing fusion proteins

include those expressing  $\beta$ -galactosidase, glutathione-S-transferase, and luciferase.

Examples of vectors include plasmid vectors (e.g., pBluescript SK(-), pBluescript SK(+), pGEX-4T, pGEX-5T, pRIT2T, pBPV, and pSVK3 (Pharmacia, etc.); ZAP Express, pYEura3, pMAM, and pOG (Toyobo); pET-11a, b, c, and d, pET-20b, pET-28a, b, and c, and pET-32a and b (Novagen); pQE-10, 16, 30, 40, 50, 60, and 70 (Qiagen); virus vectors (e.g., retrovirus vectors and adenovirus vectors); and liposome vectors (e.g., cationic liposome vectors).

In order to prepare a desired protein in the host cell, the vector according to the present invention may have a sequence which regulate expression of the protein (e.g., a promoter sequence, a terminator sequence, or an enhancer sequence) or markers for selecting a host cell (e.g., a neomycin-resistant gene or a kanamycin-resistant gene). Further, the vector may have the nucleotide sequence according to the present invention in a repeated form (e.g., in a tandem form). Such additional sequences may be introduced into the vector. A host cell may be transformed by the vector by conventional methods.

The vector according to the present invention may be prepared by conventional methods and procedures of the genetic engineering field.

Examples of host cells include E. coli (e.g., SOLR, JM109, XL1-Blue MRF', and BL21(DE3)), yeast cells (e.g., YRG-2), Bacillus subtilis, animal cells (e.g., CHO cells, COS cells, human keratinocytes, COP-5, C127, mouse 3T3 cells, FR3T3, and HB101).

The protein according to the present invention is obtained from the culture by culturing host cells which are transformed as described above in an appropriate medium. Therefore, the present invention provides a process for preparing the protein according to the present invention. Such a process enables mass production of an antitumor protein.

The culture of the transformed host cell and culture

condition may essentially be the same as those for the cell to be used. In addition, the protein according to the present invention may be recovered from the culture medium and purified according to conventional methods, for example, chromatography such as ion exchange chromatography, gel filtration chromatography, and immunoaffinity chromatography

#### Antibody

The present invention provides an antibody against the protein according to the present invention. The term "antibody" as used herein includes a polyclonal antibody or a monoclonal antibody.

The antibody according to the present invention can be prepared by conventional methods, for example, by injecting the protein of SEQ ID NO.1 or a fragment thereof into an animal (e.g., rabbit, rat or mouse) together with suitable carriers (e.g., Freund's complete and incomplete adjuvants) and then purifying the serum from the animal after a certain period.

Specific reaction (i.e., immuno reaction) of the antibody may be used as an indicator of an antitumor protein. Therefore, the antibody according to the present invention may be used for purifying and screening an antitumor protein.

#### Examples

The present invention is further illustrated by the following Examples which are not intended as a limitation of the invention.

##### Example 1 Purification of Antitumor Protein

###### (1) Purification of Protein

An antitumor protein was purified from commercially available (or wild) fresh Tricholoma matsutake by homogenizing it in accordance with conventional methods and then isolating using purifying procedures such as column chromatography, HPLC, and electrophoresis. The detailed procedure is as follows:

A Tris buffer solution containing NaCl and protease

inhibitor (50 mM Tris-HCl (pH 7.5), 150 mM NaCl, 1 mM PMSF, 1 mM EDTA, 0.1 mM IAA (iodoacetamide), 1 µg/ml pepstatin A, and 1 µg/ml leupeptin) was used for the preliminary elution of the protein, followed by precipitation with ammonium sulfate (90% saturated ammonium sulfate). The precipitate was dialyzed with 25 mM Tris-HCl (pH 7.5) containing 1/10 the above protease inhibitor (PI) to desalt. Then, after DEAE Toyopearl (ion exchange chromatography), concentration of the active fraction, purification through phenyl Sepharose (hydrophobic chromatography), concentration of the active fraction, gel filtration by HPLC (TSK gel G3000SW), the purified protein was finally obtained.

In ion exchange chromatography and hydrophobic chromatography, 25 mM Tris-HCl (pH 7.5) containing PI was used as eluant. For linear concentration gradient, NaCl and  $(\text{NH}_4)_2\text{SO}_4$  were used, respectively. In gel filtration, 0.1 M sodium phosphate buffer (pH 7.2) containing 0.1 M  $\text{Na}_2\text{SO}_4$  and PI was used as eluant.

The sample obtained by gel filtration with HPLC was analyzed by SDS-PAGE. The protein on the gel, which was transferred to a PVDF membrane and stained with CBB, exhibited a single band (about 65 kDa).

It was found that when Tricholoma matsutake with no freshness was used or when no protease inhibitor was used in purifying procedures, yield and antitumor activity were found to be lower.

Some of the samples were recovered by staining the gel with CBB after SDS-PAGE, and cutting it to extract electrically. These samples were used to determine the amino acid sequence (Example 2).

It was also found that the protein can be purified by affinity chromatography using a column in which the antibody (see (2)) was bound to CNBr-activated Sepharose 6MB resin (Pharmacia).

(2) Polyclonal Antibody



A rabbit was immunized with the protein purified in (1) to prepare antiserum. The procedure is as follows:

The purified protein, 15  $\mu$ g, was mixed with Freund's complete adjuvant, stirred intensely to emulsion, and subcutaneously injected to the back of a rabbit. After 3 weeks, the rabbit was boosted with 150  $\mu$ g of the purified protein, which was mixed with Freund's incomplete adjuvant to give emulsion. Then, after 2 weeks, they were directly reboosted using 50  $\mu$ g of antibody, and blood was collected from its earlobe 1 week later.

Next, 5 ml of antiserum was incubated at 56°C for 30 min, mixed with 5 ml of PBS(-) and the same amount of saturated  $(\text{NH}_4)_2\text{SO}_4$ , and maintained still in iced water. After centrifugation, the precipitate was redissolved in sodium phosphate buffer solution and mixed with an additional amount of saturated  $(\text{NH}_4)_2\text{SO}_4$  to a final  $(\text{NH}_4)_2\text{SO}_4$  concentration of 20%. After centrifugation, the supernatant was recovered and mixed with an additional amount of saturated  $(\text{NH}_4)_2\text{SO}_4$  to a final  $(\text{NH}_4)_2\text{SO}_4$  concentration of 33%. After centrifugation, the precipitate was recovered and redissolved. It was then dialyzed and desalted, followed by ion exchange chromatography (DE52 resin), to give an IgG fraction.

### (3) Antitumor Activity Test

Lethal activity was investigated on cells which had been transformed by simian virus 40 (SV40) and human papilloma virus (HPV) which were known to cause malignant alteration. More specifically, antitumor activity was estimated with lethal activity. When the protein purified in (1) above was given to the cells, the quantity of the tested protein necessary for 50% fatal activity of total cells was 10 ng/ml in SVT2 cells (transformed SV40 cells), 100 ng/ml in A31 cells (transformed SV40 cells), and 15-20 ng/ml in human preputial cells (transformed HPV16 cells).

### Example 2 cDNA Cloning and Sequencing

The amino acid sequence at the N-terminal of the

protein purified in Example 1 was determined (SEQ ID NOS.3 and 4) using a protein sequencer (Hewlett-Packard).

Also, the protein obtained in Example 1 was digested using lysyl endonuclease to give a number of peptide fragments. Among them, the amino acid sequences of 14 peptide fragments were determined (SEQ ID NOS.5-18).

On the other hand, Tricholoma matsutake mRNA was purified with oligo-dT Latex (oligo-dT particles; Takara), then with STRATAGENE ZAP-cDNA Synthesis Kit (available from Toyobo), to synthesize cDNA. After synthesized, the cDNA was packaged in vitro in lambda phage using Gigapak III Gold (Stratagene, available from Toyobo) to prepare a phage library.

Using the antibody obtained in Example 1 (2) as a probe, the phage library was screened for the antitumor gene. Twenty-one phages were tested positive. The procedure is as follows:

The concentration of the library was determined with titer. About 2,000 to 20,000 phages and 600 $\mu$ l E. coli (XL1-Blue) were plated in 150 mm NZYM culture plates together with 6ml NZYM Top Agar (0.7%). They were incubated at 42°C for 3-4 hours until plaques developed to suitable sizes of about 1 mm. Then, a 130-140 mm nitrocellulose membrane soaked with 10 mM IPTG was placed on each plate, and incubation was continued at 37°C for 3 hours. After the plates were cooled at 4°C for 1 hour or more, the nitrocellulose filters were removed from the plates, and shaken in TBS-T buffer solution containing 3% skim milk.

Next, the filters were soaked in the buffer solution of the primary antibody (Example 1 (2)), and gently shaken in TBS-T buffer solution containing 3% skim milk. The filters were then soaked in the buffer solution of secondary antibody conjugated to alkali phosphatase (AP), and washed with TBS-T buffer solution. After they were washed with alkali phosphatase (AP) buffer solution, positive phages were detected.

The resulting positive phages were transformed with SOLR strains (Stratagene) by in vivo excision, using ZAP-cDNA Synthesis Kit (available from Toyobo) according to a manufacturer's manual.

- 5 Plasmid pTS18 as shown in Fig. 1 was obtained from the transformants. Plasmid pTS18 (containing the cDNA sequence in SEQ ID NO. 1) was used in Example 3 as an expression vector.

- 10 The resulting pTS18 was deleted by using Exo/Mung DNA Sequencing System (Stratagene), blunted at both terminals, and ligated with self-DNA (Fig. 2). Next, E. coli JM109 (Toyobo) was transformed with the deleted plasmid DNA. The nucleotide sequences of the portions of the gene into which deletion mutation was introduced were completely determined  
15 using ABI PRISM Cycle Sequencing Kit (Parkin Elmer) both on the sense and anti-sense chains.

- The determined partial sequences were used to establish the complete amino acid sequence and cDNA sequence (SEQ ID NO.2) of the antitumor protein. A deduced molecular weight  
20 was about 62 kDa. The amino acid sequence on the N terminal (SEQ ID NOS.3 and 4) agreed with the amino acid sequence 2-30 and the amino acid sequence 2-58 in SEQ ID NO.1.

- 25 Also, the sequences of the peptide fragments (SEQ ID NOS.5-18) agreed with the amino acid sequence in SEQ ID NO.1 as follows:

- SEQ ID NO.5: 59-77 in SEQ ID NO.1;  
SEQ ID NO.6: 89-149 in SEQ ID NO.1;  
SEQ ID NO.7: 150-178 in SEQ ID NO.1;  
30 SEQ ID NO.8: 179-209 in SEQ ID NO.1;  
SEQ ID NO.9: 210-267 in SEQ ID NO.1;  
SEQ ID NO.10: 268-297 in SEQ ID NO.1;  
SEQ ID NO.11: 298-355 in SEQ ID NO.1;  
SEQ ID NO.12: 356-406 in SEQ ID NO.1;  
35 SEQ ID NO.13: 407-436 in SEQ ID NO.1;  
SEQ ID NO.14: 437-486 in SEQ ID NO.1;  
SEQ ID NO.15: 487-521 in SEQ ID NO.1;

SEQ ID NO.16: 522-554 in SEQ ID NO.1;

SEQ ID NO.17: 555-566 in SEQ ID NO.1;

SEQ ID NO.18: 78-99 in SEQ ID NO.1.

- 5        These peptide fragments are useful as antigens for obtaining an antibody against the antitumor protein which can be used in a method for screening and purifying an antitumor protein.

Example 3 Production of Antitumor Protein (1)

- 10        Competent cells (JM109 strain; Toyobo) stored at -80°C were melted, and 100 µl of the cells was transferred to Falcon tube (code 2059). It was mixed with deleted clones of pTS18 (Example 2) and allowed to stand in iced water for 30 min. After exposed to a thermal shock (42°C) for 30 s, it was cooled in ice for 2 min. After 900 µl SOC culture  
15        was added, it was incubated at 37°C for 1 hour with shaking. The cells were then planted in an LB/Amp plate in an appropriate amount, and incubated overnight at 37°C. A colony having an area of a platinum ring that appeared on the plate was transplanted to a liquid LB culture  
20        (containing Amp), and incubated at 37°C until absorption at 660 nm (Abs660) increased to about 0.2. Then, after IPTG was added to a final concentration of 10 mM, the culture was incubated until Abs660 increased to about 1.

- 25        The cells were suspended in the extract (50 mM Tris-HCl, pH 7.5) used in Example 1 (1), which contained PI, and ultrasonically destroyed. After the extract (50 mM Tris-HCl) was centrifuged, the supernatant was recovered in the eluate via affinity chromatography (CNBr-activated Sepharose 6MB resin; Pharmacia) binding the antibody  
30        described in Example 1 (2).

- The eluate was analyzed by SDS-PAGE combined with Western blotting using the antibody described in Example 1 (2). The result showed that the protein according to the present invention was expressed in the host cell.

- 35        Example 4 Production of Antitumor Protein (2)

(1) Preparation of expression vector pET-28a

A DNA fragment encoding the antitumor protein was generated by polymerase chain reaction (PCR) using plasmid pTS18 (10 ng)(Example 2) as a template DNA. PCR reaction was carried out using reagents packaged in a commercially available kit (TAKARA Co.) and the following primers (5 pmole, each) in accordance with a manufacturer's manual.

Primer 1: GAGAGACCATGGGGTATCGTCTTTCC (SEQ ID NO.19)

Primer 2: GAGAGAGGATCCGGAGACGCCAAGGAT (SEQ ID NO.20)

After the PCR reaction, the product was digested by NcoI and BamHI. The resulting fragment (0.1  $\mu$ g) was ligated into the NcoI/BamHI site of pET-28a (0.5  $\mu$ g) (Novagen).

The resulting DNA construct was introduced into competent cells (E. Coli, DH5 $\alpha$  and JM109 strains; Toyobo). The plasmid DNA which was harvested from the transformed cells was introduced into competent cells (BL21 (DE3) strain; Novagen).

#### (2) Preparation of expression vector pET-28b

A DNA fragment encoding the antitumor protein was prepared by digesting plasmid pTS18 (Example 2) by EcoRI and XhoI and collecting EcoRI/XhoI fragments. The resulting fragments (0.1  $\mu$ g) were ligated into the EcoRI/XhoI site of pET-28b (0.5  $\mu$ g)(Novagen).

The resulting DNA construct was introduced into competent cells (E. Coli, DH5 $\alpha$  and JM109 strains; Toyobo). The plasmid DNA which was harvested from the transformed cells was introduced into competent cells (BL21 (DE3) strain; Novagen).

#### (3) Expression of antitumor protein gene

One loopful of the transformed cells, BL21 (DE3) strain having pET-28a and BL21 (DE3) strain having pET-28b, obtained as described in Example 3 (1) and (2) were inoculated on 1 ml of NZYM medium containing 50  $\mu$ g/ml of Kanamycin and preincubated at 37°C overnight. 100  $\mu$ l taken from the cultured medium was inoculated on 10 ml of NZYM medium containing 50  $\mu$ g/ml of kanamycin and incubated at 25°C until Abs600 increased to about 0.4. After IPTG was

added to a final concentration of 1.0 mM, the culture was incubated for 24 hours.

The cells were harvested from the culture medium, suspended in the extract (25 mM Tris-HCl, pH 7.0) used in Example 1 (1) containing PI, and ultrasonically destroyed.

After the extract (25 mM Tris-HCl, pH 7.0) was centrifuged, the precipitate was recovered. The precipitate was analyzed by SDS-PAGE. A single band was observed on the position of 65 kDa.

The precipitate was also analyzed by Western blotting using the antibody described in Example 1 (2). An immunoreactive band was observed at the same position as that observed on the SDS-PAGE gel. This result showed that the gene of the antitumor protein was expressed in the host cells.

SEQUENCE LISTING

SEQ ID NO.1

SEQUENCE LENGTH: 556

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: protein

SEQUENCE DESCRIPTION

Met	Pro	Ile	Arg	Leu	Ser	Lys	Glu	Lys	Ile	Asn	Asp	Leu	Leu	Gln	Arg
1				5					10					15	
Ser	Gln	Gly	Asp	Leu	Thr	Ser	Ser	Gln	His	Glu	Ile	Val	His	Phe	Thr
			20					25					30		
Asp	Val	Phe	Ile	Ala	Gly	Ser	Gly	Pro	Ile	Ser	Cys	Thr	Tyr	Ala	Arg
		35					40					45			
His	Ile	Ile	Asp	Asn	Thr	Ser	Thr	Thr	Lys	Val	Tyr	Met	Ala	Glu	Ile
	50					55					60				
Gly	Ser	Gln	Asp	Asn	Pro	Val	Ile	Gly	Ala	His	His	Lys	Asn	Ser	Ile
	65					70				75				80	
Lys	Phe	Gln	Lys	Asp	Ile	Asp	Lys	Phe	Val	Asn	Ile	Ile	Asn	Gly	Ala
			85						90					95	
Leu	Gln	Pro	Ile	Ser	Ile	Ser	Pro	Ser	Asp	Thr	Tyr	Gln	Pro	Thr	Leu
			100					105					110		
Ala	Val	Ala	Ala	Trp	Ala	Pro	Pro	Ile	Asp	Pro	Ala	Glu	Gly	Gln	Leu
		115					120					125			
Val	Ile	Met	Gly	His	Asn	Pro	Asn	Gln	Glu	Ala	Gly	Leu	Asn	Leu	Pro
	130					135					140				
Gly	Ser	Ala	Val	Thr	Arg	Thr	Val	Gly	Gly	Met	Ala	Thr	His	Trp	Thr
	145				150					155				160	
Cys	Ala	Cys	Pro	Thr	Pro	His	Asp	Glu	Glu	Arg	Val	Asn	Asn	Pro	Val
				165					170					175	
Asp	Lys	Gln	Glu	Phe	Asp	Ala	Leu	Leu	Glu	Arg	Ala	Lys	Thr	Leu	Leu
			180					185					190		
Asn	Val	His	Ser	Asp	Gln	Tyr	Asp	Asp	Ser	Ile	Arg	Gln	Ile	Val	Val
	195						200					205			
Lys	Glu	Thr	Leu	Gln	Gln	Thr	Leu	Asp	Ala	Ser	Arg	Gly	Val	Thr	Thr
	210					215						220			

	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429
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Thr Ser Val Ala Asp Pro Thr Ser Lys Val His Asn Phe Asn Asn Leu
515                               520                               525
Trp Val Gly Gly Asn Gly Cys Ile Pro Asp Ala Thr Ala Cys Asn Pro
530                               535                               540
Thr Arg Thr Ser Val Ala Tyr Ala Leu Lys Gly Ala Glu Ala Val Val
545                               550                               555                               560
Asn Tyr Leu Gly Val Ser      *
565

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## SEQ ID NO.2

SEQUENCE LENGTH: 1701

SEQUENCE TYPE: nucleic acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: cDNA to RNA

## SEQUENCE DESCRIPTION

```

ATG CCG ATA CGT CTT TCC AAA GAA AAA ATC AAC GAC CTG CTG CAA CGT      48
Met Pro Ile Arg Leu Ser Lys Glu Lys Ile Asn Asp Leu Leu Gln Arg
1           5           10           15
TCT CAA GGG GAT CTT ACT TCC TCG CAA CAC GAA ATT GTA CAT TTC ACT      96
Ser Gln Gly Asp Leu Thr Ser Ser Gln His Glu Ile Val His Phe Thr
20           25           30
GAT GTT TTC ATT GCT GGC AGT GGT CCC ATT AGC TGT ACT TAC GCC CGC      144
Asp Val Phe Ile Ala Gly Ser Gly Pro Ile Ser Cys Thr Tyr Ala Arg
35           40           45
CAC ATC ATT GAC AAT ACC TCA ACT ACA AAG GTT TAC ATG GCC GAA ATA      192
His Ile Ile Asp Asn Thr Ser Thr Thr Lys Val Tyr Met Ala Glu Ile
50           55           60
GGT TCT CAA GAT AAC CCT GTC ATC GGG GCC CAT CAC AAG AAC TCC ATA      240
Gly Ser Gln Asp Asn Pro Val Ile Gly Ala His His Lys Asn Ser Ile
65           70           75           80
AAG TTT CAG AAA GAC ATT GAC AAG TTT GTG AAT ATC ATC AAC GGT GCC      288
Lys Phe Gln Lys Asp Ile Asp Lys Phe Val Asn Ile Ile Asn Gly Ala
85           90           95

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CTC	CAG	CCG	ATT	TCG	ATT	TCG	CCA	TCG	GAC	ACC	TAC	CAG	CCC	ACT	CTC	336
Leu	Gln	Pro	Ile	Ser	Ile	Ser	Pro	Ser	Asp	Thr	Tyr	Gln	Pro	Thr	Leu	
			100					105					110			
GCT	GTA	GCA	GCG	TGG	GCG	CCG	CCC	ATC	GAT	CCT	GCC	GAA	GGC	CAG	CTC	384
Ala	Val	Ala	Ala	Trp	Ala	Pro	Pro	Ile	Asp	Pro	Ala	Glu	Gly	Gln	Leu	
			115					120					125			
GTG	ATT	ATG	GGA	CAC	AAT	CCG	AAT	CAG	GAG	GCC	GGC	CTG	AAC	CTT	CCC	432
Val	Ile	Met	Gly	His	Asn	Pro	Asn	Gln	Glu	Ala	Gly	Leu	Asn	Leu	Pro	
			130					135					140			
GGT	AGC	GCT	GTC	ACT	AGG	ACA	GTC	GGG	GGG	ATG	GCG	ACC	CAC	TGG	ACT	480
Gly	Ser	Ala	Val	Thr	Arg	Thr	Val	Gly	Gly	Met	Ala	Thr	His	Trp	Thr	
			145					150			155				160	
TGC	GCG	TGT	CCT	ACT	CCA	CAT	GAC	GAA	GAG	AGG	GTC	AAC	AAC	CCA	GTT	528
Cys	Ala	Cys	Pro	Thr	Pro	His	Asp	Glu	Glu	Arg	Val	Asn	Asn	Pro	Val	
								165			170				175	
GAC	AAG	CAG	GAG	TTC	GAC	GCA	CTG	CTC	GAA	CGT	GCT	AAA	ACA	TTG	CTC	576
Asp	Lys	Gln	Glu	Phe	Asp	Ala	Leu	Leu	Glu	Arg	Ala	Lys	Thr	Leu	Leu	
								180							190	
AAC	GTT	CAC	AGC	GAC	CAG	TAC	GAC	GAT	TCT	ATC	CGT	CAG	ATA	GTT	GTC	624
Asn	Val	His	Ser	Asp	Gln	Tyr	Asp	Asp	Ser	Ile	Arg	Gln	Ile	Val	Val	
								195							205	
AAA	GAG	ACT	CTT	CAG	CAG	ACC	CTT	GAT	GCG	TCG	CGG	GGT	GTG	ACC	ACT	672
Lys	Glu	Thr	Leu	Gln	Gln	Thr	Leu	Asp	Ala	Ser	Arg	Gly	Val	Thr	Thr	
								210							220	
CTC	CCG	CTG	GGG	GTG	GAG	CGC	CGT	ACG	GAC	AAT	CCT	ATT	TAT	GTC	ACC	720
Leu	Pro	Leu	Gly	Val	Glu	Arg	Arg	Thr	Asp	Asn	Pro	Ile	Tyr	Val	Thr	
								225							240	
TGG	ACC	GGT	GCC	GAT	ACC	GTC	CTT	GGT	GAT	GTG	CCG	AAG	AGT	CCC	CGA	768
Trp	Thr	Gly	Ala	Asp	Thr	Val	Leu	Gly	Asp	Val	Pro	Lys	Ser	Pro	Arg	
								245							255	
TTC	GCT	TTG	GTT	ACA	GAG	ACG	AGA	GTG	ACG	AAG	CTT	ATT	GTC	AGT	GAA	816
Phe	Ala	Leu	Val	Thr	Glu	Thr	Arg	Val	Thr	Lys	Leu	Ile	Val	Ser	Glu	
								260							270	
ACC	AAT	CCG	ACG	CAG	GTT	GTT	GCT	GCG	TTG	CTA	CGT	AAC	TTG	AAT	ACA	864
Thr	Asn	Pro	Thr	Gln	Val	Val	Ala	Ala	Leu	Leu	Arg	Asn	Leu	Asn	Thr	
								275							285	

AGC AAC GAT GAA CTT GTC GTG GCC AAG AGT TTC GTC ATA GCT TGT GGA	912
Ser Asn Asp Glu Leu Val Val Ala Lys Ser Phe Val Ile Ala Cys Gly	
290 295 300	
GCA GTC TGC ACA CCG CAA ATC TTG TGG AAC AGC AAC ATC CGC CCA TAT	960
Ala Val Cys Thr Pro Gln Ile Leu Trp Asn Ser Asn Ile Arg Pro Tyr	
305 310 315 320	
GCG CTT GGT CGC TAC CTC AGC GAA CAG TCC ATG ACT TTT TGT CAG ATC	1008
Ala Leu Gly Arg Tyr Leu Ser Glu Gln Ser Met Thr Phe Cys Gln Ile	
325 330 335	
GTT CTC AAG AGG GGC ATA GTC GAT GCC ATC GCT ACT GAC CCT CGC TTC	1056
Val Leu Lys Arg Gly Ile Val Asp Ala Ile Ala Thr Asp Pro Arg Phe	
340 345 350	
GCT GCG AAG GTT GAG GCG CAC AAG AAG CAC CCC GAT GAC GTG CTG	1104
Ala Ala Lys Val Glu Ala His Lys Lys His Pro Asp Asp Val Leu	
355 360 365	
CCC ATT CCA TTC CAC GAG CCT GAA CCT CAA GTG ATG ATT CCG TAC ACG	1152
Pro Ile Pro Phe His Glu Pro Glu Pro Gln Val Met Ile Pro Tyr Thr	
370 375 380	
TGC GAC TTC CCT TGG CAT GTT CAG GTG CAT CGC GAT GCA TTC TCA TAT	1200
Ser Asp Phe Pro Trp His Val Gln Val His Arg Asp Ala Phe Ser Tyr	
385 390 395 400	
GGT GAT GTT GGA CCC AAG GCC GAC CCG CGT GTT GTC GTC GAT CTG AGG	1248
Gly Asp Val Gly Pro Lys Ala Asp Pro Arg Val Val Val Asp Leu Arg	
405 410 415	
TTT TTC GGC AAA TCA GAT ATT GTC GAA GAA AAT CGA GTG ACT TTC GGT	1296
Phe Phe Gly Lys Ser Asp Ile Val Glu Glu Asn Arg Val Thr Phe Gly	
420 425 430	
CCG AAC CCT AAG CTA CGC GAG TGG GAA GCG GGT GTT ACA GAC ACT TAT	1344
Pro Asn Pro Lys Leu Arg Glu Trp Glu Ala Gly Val Thr Asp Thr Tyr	
435 440 445	
GGA ATG CCA CAG CCG ACA TTC CAT GTC AAG CGG ACC AAC GCC GAT GGA	1392
Gly Met Pro Gln Pro Thr Phe His Val Lys Arg Thr Asn Ala Asp Gly	
450 455 460	
GAC CGT GAC CAG AGG ATG ATG AAT GAT ATG ACC AAC GTC GCG AAC ATG	1440
Asp Arg Asp Gln Arg Met Met Asn Asp Met Thr Asn Val Ala Asn Met	
465 470 475 480	

CTG GGT GGG TAC CTT CCT GGC TCC TAC CCT CAA TTT ATG GCA CCT GGT 1488  
 Leu Gly Gly Tyr Leu Pro Gly Ser Tyr Pro Gln Phe Met Ala Pro Gly

485

490

495

CTC GTA CTG CAC ATC ACG GGA ACT ACT CGG ATC GGG ACA GAT GAT CAA 1536  
 Leu Val Leu His Ile Thr Gly Thr Thr Arg Ile Gly Thr Asp Asp Gln

500

505

510

ACT TCT GTT GCT GAT CCG ACA TCA AAG GTT CAT AAC TTC AAC AAT CTG 1584  
 Thr Ser Val Ala Asp Pro Thr Ser Lys Val His Asn Phe Asn Asn Leu

515

520

525

TGG GTC GGC GGG AAT GGG TGC ATT CCA GAT GCG ACT GCC TGC AAC CCG 1632  
 Trp Val Gly Gly Asn Gly Cys Ile Pro Asp Ala Thr Ala Cys Asn Pro

530

535

540

ACT CGT ACG AGC GTC GCG TAT GCG CTC AAG GGT GCT GAG GCT GTA GTC 1680  
 Thr Arg Thr Ser Val Ala Tyr Ala Leu Lys Gly Ala Glu Ala Val Val

545

550

555

560

AAT TAC CTT GGC GTC TCC TGA 1701  
 Asn Tyr Leu Gly Val Ser \*

565

SEQ ID NO.3

SEQUENCE LENGTH: 29

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Pro Ile Arg Leu Ser Lys Glu Lys Ile Asn Asp Leu Leu Gln Arg Ser

1

5

10

15

Gln Gly Asp Leu Thr Ser Ser Gln His Glu Ile Val His

20

25

SEQ ID NO.4

SEQUENCE LENGTH: 57

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

```

Pro Ile Arg Leu Ser Lys Glu Lys Ile Asn Asp Leu Leu Gln Arg Ser
 1             5             10             15
Gln Gly Asp Leu Thr Ser Ser Gln His Glu Ile Val His Phe Thr Asp
      20             25             30
Val Phe Ile Ala Gly Ser Gly Pro Ile Ser Cys Thr Tyr Ala Arg His
      35             40             45
Ile Ile Asp Asn Thr Ser Thr Thr Lys
      50             55

```

SEQ ID NO.5

SEQUENCE LENGTH: 19

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

```

Val Tyr Met Ala Glu Ile Gly Ser Gln Asp Asn Pro Val Ile Gly Ala
 1             5             10             15
His His Lys

```

SEQ ID NO.6

SEQUENCE LENGTH: 61

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Phe	Val	Asn	Ile	Ile	Asn	Gly	Ala	Leu	Gln	Pro	Ile	Ser	Ile	Ser	Pro
1					5					10					15
Ser	Asp	Thr	Tyr	Gln	Pro	Thr	Leu	Ala	Val	Ala	Ala	Trp	Ala	Pro	Pro
			20					25						30	
Ile	Asp	Pro	Ala	Glu	Gly	Gln	Leu	Val	Ile	Met	Gly	His	Asn	Pro	Asn
			35					40					45		
Gln	Glu	Ala	Gly	Leu	Asn	Leu	Pro	Gly	Ser	Ala	Val	Thr			
			50				55					60			

SEQ ID NO.7

SEQUENCE LENGTH: 29

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Arg	Thr	Val	Gly	Gly	Met	Ala	Thr	His	Trp	Thr	Cys	Ala	Cys	Pro	Thr
1					5					10				15	
Pro	His	Asp	Glu	Gly	Arg	Val	Asn	Asn	Pro	Val	Asp	Lys			
			20						25						

20                      25                      30

50 55

SEQ ID NO.10

SEQUENCE LENGTH: 30

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Leu	Ile	Val	Ser	Glu	Thr	Asn	Pro	Thr	Gln	Val	Val	Ala	Ala	Leu	Leu
1					5				10					15	
Arg	Asn	Leu	Asn	Thr	Ser	Asn	Asp	Glu	Leu	Val	Val	Ala	Lys		
			20					25					30		

SEQ ID NO.11

SEQUENCE LENGTH: 58

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Ser	Phe	Val	Ile	Ala	Cys	Gly	Ala	Val	Cys	Thr	Pro	Gln	Ile	Leu	Trp
1					5					10				15	
Asn	Ser	Asn	Ile	Arg	Pro	Tyr	Ala	Leu	Gly	Arg	Tyr	Leu	Ser	Glu	Gln
			20					25				30			
Ser	Met	Thr	Phe	Cys	Gln	Ile	Val	Leu	Lys	Arg	Gly	Ile	Val	Asp	Ala
			35					40				45			
Ile	Ala	Thr	Asp	Pro	Arg	Phe	Ala	Ala	Lys						
			50					55							



SEQ ID NO.12

SEQUENCE LENGTH: 51

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Val	Glu	Ala	His	Lys	Lys	Lys	His	Pro	Asp	Asp	Val	Leu	Pro	Ile	Pro
1				5					10					15	
Phe	His	Glu	Pro	Glu	Pro	Gln	Val	Met	Ile	Pro	Tyr	Thr	Ser	Asp	Phe
			20					25						30	
Pro	Trp	His	Val	Gln	Val	His	Arg	Asp	Ala	Phe	Ser	Tyr	Gly	Asp	Val
			35				40						45		
Gly	Pro	Lys													
			50												

SEQ ID NO.13

SEQUENCE LENGTH: 30

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Ala	Asp	Pro	Arg	Val	Val	Val	Asp	Leu	Arg	Phe	Phe	Gly	Lys	Ser	Asp
1				5					10					15	
Ile	Val	Glu	Glu	Asn	Arg	Val	Thr	Phe	Gly	Pro	Asn	Pro	Lys		
			20					25					30		

SEQ ID NO.14

SEQUENCE LENGTH: 50

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Leu Arg Glu Trp Glu Ala Gly Val Thr Asp Thr Tyr Gly Met Pro Gln

1

5

10

15

Pro Thr Phe His Val Lys Arg Thr Asn Ala Asp Gly Asp Arg Asp Gln

20

25

30

Arg Met Met Asn Asp Met Thr Asn Val Ala Asn Met Leu Gly Gly Tyr

30

40

45

Leu Pro

50

SEQ ID NO.15

SEQUENCE LENGTH: 35

SEQUENCE TYPE: amino acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION

Gly Ser Tyr Pro Gln Phe Met Ala Pro Gly Leu Val Leu His Ile Thr

1

5

10

15

Gly Thr Thr Arg Ile Gly Thr Asp Asp Gln Thr Ser Val Ala Asp Pro

20

25

30

Thr Ser Lys

35

Lys

1                      5                      10

20

SEQ ID NO.19

SEQUENCE LENGTH: 26

SEQUENCE TYPE: nucleic acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: synthetic DNA

SEQUENCE DESCRIPTION

GAGAGACCAT GGGGTATCGT CTTTCC

26

SEQ ID NO.20

SEQUENCE LENGTH: 27

SEQUENCE TYPE: nucleic acid

STRANDNESS: single

TOPOLOGY: linear

MOLECULE TYPE: synthetic DNA

SEQUENCE DESCRIPTION

GAGAGAGGAT CCGGAGACGC CAAGGAT

27